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Diagnostic Brain Biopsy - 15 year Experience at NIMHANS

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T Asha, S K Shankar ,

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, Sarala Das, T Vasudev Rao, Y Ramamohan, K R Vani,

- *Department of Neuropathology, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

D Nagaraja, S. R. Aroor, - *Department of Neurology, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

V Ravi, - *Department of Neurovirology, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

K Taranatha Shetty, - *Department of Neurochemistry, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

B A Chandramouli, - *Department of Neurosurgery, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

Abstract

Brain biopsy is one of the important investigative procedures for establishing a diagnosis in various progressive diseases of the nervous system. At present with the availability of more modern and sophisticated techniques, the need for sampling brain is becoming limited. However, in a few conditions it remains the only method for establishing the diagnosis. We have reevaluated 71 brain biopsies performed during the past 15 years regarding the diagnostic usefulness. In 48 cases a definite diagnosis could be made, 16 biopsies were abnormal but no definite diagnosis could be offered, while 5 biopsies were within normal limits. In two cases, the biopsy material was inadequate for study. Majority of the biopsies with definite diagnostic pathology were from cases of SSPE. The other conditions diagnosed histopathologically include dysmyelinating and demyelinating conditions like, Schilder's disease, Krabbe's disease, Canavan's disease, sundanophillicleukodystrophy, degenerate conditions like Lafora body disease, Creutzfeldt Jakob disease and Viral encephalitis of herpes simplex type. A multi disciplinary approach in study has helped in improving the diagnostic efficiency and evolving other modalities of investigations to limit the procedure of brain biopsy to only conditions, with no other alternative diagnostic procedure.

Key words -

Brain biopsy,
Neurodegenerative conditions,
SSPE,
Canavan's disease,
Schilder's disease,
Leukodystrophy,

Foerster [1], in 1912, introduced the procedure of brain biopsy and emphasised its value in the diagnostic aramantarium of the neurophysician. Despite the hopes extended by McMenemy [2], [3] the brain biopsy as an established method of diagnosis in most advanced neurological centres in the world, it has not received enough attention. This is because of the bias and the fear of "alleged hazards" to the patient and to the operating surgeon, especially in cases of slow virus diseases [4].

In general, cerebral biopsy is performed in a disease, that is progressive and unremitting, accompanied by dementia or drop in mental milestones [1], [2], [5], [6], [7], [8]. The procedure is chosen to achieve a diagnosis, that has eluded the clinical and routine laboratory evaluation [6], [7]. It is performed with an assumption that the disease process is likely to be diffuse and thus there is a reasonable chance of obtaining material from the "silent area" of the brain, for pathological evaluation, with minimal or no morbidity to the patient [4], [9], [10]. In cases of cerebral degeneration, definite diagnosis is needed, not only to evaluate prognosis of the disease, but also to offer guidance and genetic counselling to parents [1], [2], [4], [5], [6], [8]. To the best of our knowledge, only two studies on brain biopsy are published from India, one essentially confined to the diagnosis of dementia in a psychiatric set up [11] and the other from a neuropathology department [12], [13].

In his very early studies, before the recommendations of the 1965 Neuropathology Congress, Dastur in Bombay had utilised mainly brain biopsy material in reporting the entities of "Tuberculosis encephalopathy" [12] and subacute "gliosing panencephalitis" [13]. He has stressed the necessity of a nontraumatised, noncogulated, full thickness brain biopsy including both grey and white matter, preferably from the nondominant frontal lobe, and the importance of a neurosurgeon trained in the procedure. The present communication documents our experience with diagnostic brain biopsies over a 15 year period (1976-1989) at National Institute of Mental Health & Neuro Sciences, Bangalore .

Material and Methods

The study is based on 71 biopsies received between 1976 and 1989 which includes brain biopsies referred from other centres. Brain biopsy was contemplated only when all other available investigative facilities had failed to give a diagnostic clue. The procedure was always performed after obtaining a written consent from next to kin as per the rules of the hospital. The brain tissue was collected by a regular craniotomy or through a trephine craniotomy. Biopsies of tumours presenting as mass lesions were excluded from the study. The data were collected retrospectively from the clinical records. All the brain biopsies were reviewed independently by two of the authors (TA and SKS) and correlated with the clinical data to arrive at pathological features. After recording the pathological features, the findings were correlated with various virological, serological and other laboratory data.

The indications for brain biopsy were chronic, bilateral cerebral involvement with progressive dementia; or mental retardation/drop in mental and physical milestones in paediatric cases, or acute unilateral/bilateral cerebral involvement indicating a meninogoencephalitic process.

Paraffin sections from all the biopsies were routinely stained with HE, cresylviolet, LFB, PAS, PTAH and Bodian silver, to visualise various elements of the nervous tissue. Whenever necessary, frozen sections were stained with oil red 'O' for neutral lipids. Loyez for myelin, Cajal for hypertrophic astrocytes and Hortega's silver carbonate for microglia.

Twenty-one of the specimens were examined by electron microscopy. Forty-eight biopsies revealed features supportive or confirmative of the diagnosis while 21 were not contributory to establish a definitive pathological diagnosis. In two of the patients, suspected of having herpes simplex encephalitis, the biopsy was subjected to immunohistochemical staining for localisation of viral

antigen, using polyclonal rabbit antiserum (DACOPAT immunochemicals, USA). Paraffin sections of the brain biopsy from 23 patients diagnosed to have SSPE, have been stained similarly by immunohistochemical technique, utilising high titre CSF from a proven case of measles as the source of primary antibody, to localise the viral antigen intracellualrly. Co-cultivation of fresh, dissociate, brain biopsy suspension with a permissive cell line was done in one case of SSPE to identify the virus by cytopathic effect. The CSF samples from cases diagnosed to have SSPE have been analysed by serological methods and 'isoelectrofocussing' to detect the presence of the viral specific antibodyy and oligoclonal nature of the immuno-globulins synthesized in CSF. These findings complimented the pathological features to arrive at a definitive diagnosis.

Based on pathological features, the brain biopsies were divided into three groups

(a) diagnostic- where the features were fairly specific to be categorized into a well defined pathological entity,

(b) abnormal but not diagnostic, where some nonspecific neuropathological changes like oedema, astrocytosis, neuronmal loss and microglial reaction were noted, but the precise nature of the pathology could not be defined further and

(c) normal - where no pathological changes were evident (Table I).

Table I - Diagnositc brain biopsy

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Results

In two cases, the biopsy sample was inadequate to interpret and hence they were excluded. The data presented is based on the remaining 69 cases. Twenty-five patients were children, below 10 years of age, the rest belonged to other age groups; male; female- 43:26. The site of the brain biopsies was recorded in 31 patients. They were from the right frontal, posterior parietal, occipital and left frontal zones, in that order of frequency. In cases suspected to have herpes encephalitis, the biopsy was taken from one of the temporal lobes.

Most of the patients tolerated the operative procedure well. One patient developed CSF leak during the immediate postoperative period, which was stopped with treatment. This patient was discharged and lost for follow-up. There was no mortality or morbidity attributable to surgery. From the records, follow-up was available for 21 patients. Nine patients died within 33 days following the biopsy, among w2hich 6 patients were autopsied.

Two of the patients who were in a moribund condition before the biopsy, died within two days of the diagnostic procedure and were autopsied. The diagnoses made in these cases were viral encephalitis and SSPE respectively. The clinical condition was "status quo" in 5 patients who were followed up for varying periods, from 3 months to one and half years. Clinical improvement was noted in 7 patents. Two patents improved with specific treatment. A young girl in whom a fungal lesion was diagnosed and treated was well 3 years after the biopsy, while another man who had herpes encephalitis recovered totally and went back to his work. Others showed mild clinical improvement, probably due to autiodema measures. The rest of them were discharged from the hospital and are lost for follow-up.

Both the cases where the brain biopsy was sent for histological evaluation from other institutions were

diagnosed to have Creutzfeldt Jakob disease and they expired within a few days due to the disease.

Diagnostic Brain Biopsies

Forty-eight patients in this category belonged to the age group 1-20 years, of which 25 were below 10 year of age. The clinical diagnosis differed from the final pathological diagnosis. The clinical diagnosis entertained prior to biopsy is indicated in Table II. In the remaining 41 cases, the clinical and pathological diagnosis concurred. The diagnosis of SSPE was considered highly probable in cases where the clinical, EEG and laboratory findings were strongly indicative of it, though the intranucelar inclusions were not demonstrable. In 7 biopsies, measles viral antigen could be demonstrated intraneuronally and in oligodendroglia by immunochemical methods. The "measles like" virus was identified by co-cultivation and further confirmed by serological studies in one case. Oligoclonal bands in isoelectrofocussing were detected in 5 cases, supporting the diagnosis of SSPE. In cases of herpes encephalitis, both in CSF and tissue section, immunochemical localisation of the specific antigen confirmed the diagnosis. In two cases, where the clinical features were suggestive of dementia and herpes encephalitis respectively, the brain biopsy revealed features of a treatable disease condition. In one, a 19 year old female was diagnosed to have been suffering from dementia of unknown origin. Three of her sibs died of similar illness, one during childhood and other two in adulthood. Clinically her illness was thought to be a progressive degenerative disease. However, pathological examination of the brain biopsy showed granulomatous meningoencephalitis with multiple small abscesses, secondary to fungal infection by 'Cladosporium bantianum'. Following therapy, she is well after 3 years. In the second case, clinically diagnosed as herpes encephalitis, the brain biopsy revealed features of tuberculosis meningoencephalitis. Inspite of appropriate therapy, this patient expired a week later.

Table II - Correlation of pathological and clinical diagnosis on brain biopsy

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Clinical diagnosis considered before biopsy, is indicated in the last column (differed). Concurred clinical diagnosis prior to biopsy was the same as the final pathological diagnosis.

Abnormal, but no diagnostic pathology

Sixteen cases fall into this category. The biopsy material, both grey and white matter, showed mild glial proliferation but no other specific change to confirm the clinical diagnosis.

Normal Biopsies

Five brain biopsies were labelled as within normal histological limits. The clinical diagnosis made in these cases were Lipidosis, Leukodystrophy, Juvenile Parkinsonism and Dementia.

Discussion

This study from our Centre has amply demonstrated the usefulness of the brain biopsy as a diagnostic procedure, though discouraged and avoided by many. In addition to confirming the clinical diagnosis in many cases and thus aiding the clinician in planning the management strategies, the study has brought to light treatable conditions which otherwise could have been missed. In trophics, it is evident that many of the inflammatory conditions mimic neurodegenerative disease, thus misleading the clinician [13], [14].

The major point of discussion in performing the brain biopsy is to evolve a rationale for the procedure. Criteria must be laid down in terms of usefulness to the patient, his family and to the advancement of medical science, taking into account also the potential risks of the procedure to the patient. Following deliberations during the Fifth International Congress of Neuropathology at Zurich, Biemond [15] summarised the views of the various neurologists and neurosurgeons regarding the criteria to be fulfilled before the brain biopsy was performed as follows:

a) The Physician is convinced of the presence of a chronic, bilateraly diffuse and progressive cerebral disorder.
b) All other possible investigative methods have failed to offer a reasonable diagnosis.
c) The general condition of the patient permits the procedure and does not result in any obvious deliterious effect, on performing the biopsy on a nondominant "silent" part of the cerebral hemisphere.
d) Permission has been obtained from the patient/or relatives after the limited aim of the procedure and the limitations have been explained in detail.
e) Adequate diagnostic facilities are available for the fullest use/examination of the material obtained.

In the present series, the criteria for selection were relatively uniform, based on clinical evidence and investigations, which defied a definite diagnosis. There are proponents advocating the procedure to be performed late, where the disease has far advanced and the biopsy is unlikely to cause more deficit [13], [16]. The other school of thought advocates the biopsy to be undertaken early, so that surgical procedure does not cause tissue destruction and cloud or alter the evolution of the disease [7].

However, our experience, similar to that of Moossy [16], has shown that performing brain biopsy, following the usual criteria, even in the late stage, is useful in several ways-

1. Treatable conditions could be identified which might have been considered as a degenerative disease otherwise.
2. By offering a definite diagnosis of CJD, a slow virus disease, it was possible to offer an informed prognosis to the family and plan the course of management.
3. In paediatric cases, genetic counselling could be provided when a familial disorder was diagnosed.

In addition to offering the diagnosis, the study of brain biopsy provides great possibilities for advancing scientific knowledge to develop new diagnostic modalities and therapeutic possibilities for the future. By a multidisciplinary approach, now it has become possible to diagnose SSPE by demonstrating measles related antibodies and oligoclonal antibodies in CSF and thus avoid a brain biopsy. In cases of Lafora body disease, though initially we relied on brain biopsy to diagnose it, we have now found good success though in some cases only, in diagnosing it by axillary skin biopsy and liver biopsy as reported by others [17], [18]. However, in some instances, it is necessary to keep in mind

that only the brain tissue was positive for the Lafora bodies and not the peripheral tissues, thus necessitating brain biopsy for a firm diagnosis and family counselling. It was through detailed light microscopy of a single brain biopsy specimen that Dastur and Colleagues [19] presented the entity of "Unusual myoclonus body disease" in an adult; and using mainly electronmicroscopy they described the "late infantile form of Ceroid lipofuscinosis" [20], on the brain biopsy from another case. Hereditary enzyme deficiency states like metachromatic leukodystrophy can be diagnosed by demonstration of the abnormal storage material in the brain and also in the other peripheral tissues. Peripheral nerve, deep skin, liver and rectal biopsies are preferred now for diagnosis [3], [4], [5], [18] thus avoiding the need to sample the brain tissue.

However, in certain conditions like myelinoclastic diffuse sclerosis (Schilder's disease), Canavan's leukodystrophy, Creutzfedlt-Jakob disease and Alzheimer's disease,. study of the brain biopsy is the only mode of diagnosis [1], [2], [5], [6], [11], [21]. A multidisciplinary approach, unlike in the earlier days, has facilitated us to practice simpler diagnostic methods and avoid sampling of the brain to a large extent.

Though there is difference of opinion among the neurologists and neurosurgeons for and against the procedure, we still feel this investigative modality has a lot to offer for advancement of science and is unvoidable for diagnosis in certain cases.

The criteria for brain biopsy have significantly narrowed down with the advent of the newer techniques. It is done now when there is no alternative procedure that can establish the clinical diagnosis. In neonatal and paediatric patients, it is carried out to determine the diagnosis when the differential diagnosis considered also offer equally grave prognosis and are not usually amenable to treatment. The diagnosis will alert the parents, so that the subsequent pregnancies can be screened by various antenatal techniques in the first trimester itself, thus identifying an 'unborn patient'. The rapid strides made in molecular biology, genetic engineering and development of transgenic animals by incorporating desired genetic material, give reason for optimism in the treatment of inborn errors of metabolism in the near future. For optimal utilisation of these scientific advancements and to promote planned parentage by identifying the handicapped children with untreatable nervous disorders, the brain biopsy as a diagnositc procedure still has an important role.

Following submission of this manuscript we studied four more brain biopsies during the years 1990-1991. A definite diagnosis could be offered in all the cases viz., Balo's Concentric Sclerosis, Alzheimer's disease, Ceroid lipofuscinosis and hydrocephalus. This is the second case in World literature, where diagnosis of Balo's Concentric Sclerosis was offered on brain biopsy, in a live patient. Following steroid therapy, the patient made dramatic recovery. Brain biopsy in the case of Alzheimer's disease helped not only to confirm the diagnosis, but also identify first authentic case of familial Alzheimer's disease from India, where 4 members of the family are affected. These two cases further illustrate the paramount role of brain biopsy as a diagnostic procedure.

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